REMARKS

The Office Action of January 7, 2003 has been reviewed and the Examiner's comments carefully considered. Claims 9-11, 13-14, 16-17 and 19-20 stand rejected under 35 U.S.C. 102(b) as assertedly being anticipated by JP 08224073. Claims 9-11, 13-14, and 18-20 stand rejected under 35 U.S.C. 102(b) as assertedly being anticipated by XP-00210314. Claims 9-11, 15-18, and 19-20 stand rejected under 35 U.S.C. 102(b) as assertedly being anticipated by EP 0222257. Claims 9-11 stand rejected under 35 U.S.C. 102(b) as assertedly being anticipated by Almada et al. Claim 12 stands rejected under 35 U.S.C. 103(a) as assertedly being unpatentable over Almada et al. The Examiner asserts that composition claims that recite an intended use do not hold patentable weight. Applicant has canceled composition claims 9-12, which moots this rejection. The Examiner asserts that the JP, XP, and EP references disclose the use of creatine to recover from muscle fatigue, muscle weakness, and muscle atrophy, respectively, thus assertedly teaching the treating of muscle disuse symptoms.

The present Amendment cancels claims 9-12 and 19-20, amends claims 13 and 17, and adds claims 21 and 22. Support for the language in claim 13 is found on page 9, line 26 and page 10, lines 7-8, and 21-24. Support for the language in claim 17 is found on page 10, lines 21-24. Support for the language in claim 21 is found on page 9, lines 36-37 and page 10, lines 25-26. Support for the language of claim 22 is found on page 9, line 26 and 36-37, and page 10, lines 7-8, 21-24 and 25-26. No new matter has been added. In view of these amendments and the following explanation, Applicant believes that all the asserted rejections are in condition for withdrawal and all the claims are in condition for allowance.

The critical feature of the claimed invention, as now more particularly claimed, is the repeated administration of a creatine compound, in unit dosage form, during a period of

immobilization of a muscle and during a subsequent rehabilitation period, wherein the creatine compound dosage amount decreases substantially after the end of the immobilization period and during the rehabilitation period, and further wherein the total treatment period of creatine administration lasts up to between two and twelve weeks. Such treatment of affected musculature as claimed in the present invention results in the prevention or a substantially accelerated recovery from muscle disuse syndrome.

There are fundamental differences between the symptoms of muscle fatigue and weakness that accompany muscle disuse syndrome versus the ordinary muscle fatigue that results from normal muscle overuse. Specifically, muscle disuse syndrome is *not* characterized by normal muscle fatigue. In normal muscle fatigue, muscle contractile failure occurs predictably after muscle overload (overuse) and then recovers shortly thereafter. Rather, muscle disuse syndrome is characterized by *premature* muscle fatigue and prolonged muscle weakness, i.e., an accelerated, pronounced, protracted, and unpredictable failure of muscle contractile function that is slow to recover, if at all. The prevention and treatment of muscle disuse syndrome, with its full constellation of unique pathological properties and its own set of at-risk patients, is the focus of the claimed invention, rather than merely the treatment of normal muscle fatigue.

In contrast to the particular method of the claimed invention for treating muscle disuse syndrome, the JP and XP references teach an acute administration of creatine to recover from muscle fatigue or weakness that may result from exercise, and the EP reference neither teaches nor suggests chronic administration of creatine during an immobilization period and a rehabilitation period in which the dosage amount is substantially decreased during the rehabilitation period. Indeed, none of the cited prior art teaches or suggests the administration of

a substantial dosage of creatine during a time when a muscle is immobilized, which dosage is then decreased during rehabilitation of the affected muscle. Such a protocol, as claimed in the present invention, would indeed be counter-intuitive, and the cited prior art bolsters this point by teaching the administration of creatine only after a muscle has undergone the pathological event, i.e., immobilization, that produces the disuse syndrome, and not during the immobilization period itself. Moreover, not only is administration of creatine during immobilization not taught by the prior art, but the effective dosage amounts of creatine disclosed in the prior art remain constant throughout a given treatment protocol, rather than substantially decreasing after an immobilization period and during a rehabilitation period, as claimed in the present invention. For all the above reasons, none of the JP, XP or EP references teaches or anticipates the present invention as claimed.

Corroborating evidence for the new and unexpected results that occur when creatine is administered during the immobilization period, and then subsequently administered during the rehabilitation period at a substantially lower effective dosage amount, is provided in the enclosed scientific article entitled, *"Oral Creatine Supplementation Facilitates the Rehabilitation of Disuse Atrophy and Alters the Expression of Muscle Myogenic Factors in Humans,"* J. Physiol., 536 (2): 624-633, 2001. The article reports a double-blind study that was performed on young healthy volunteers in which their right leg was immobilized with a cast for two weeks. Thereafter, the subjects participated in a rehabilitation program lasting ten weeks. Half of the subjects received creatine and the other half received a placebo. The creatine group ingested 5 g of creatine 4 times a day during the immobilization phase. This dosage was decreased to 5 g 3 times a day for the first three weeks of rehabilitation, and further decreased to 5 g once a day for the remaining seven weeks. The results showed that chronic oral creatine

supplementation during the immobilizaton period, in which the dosage was decreased during the rehabiliation period, significantly shortened the duration of rehabilitation needed to restore muscle mass following muscle disuse atrophy and stimulated muscle hypertrophy during rehabilitation strength training compared to controls.

Further evidence of the new and unexpected results that occur when creatine is administered both during the immobilization and rehabilitation periods, and in which the effective dosage amount of creatine is decreased substantially during the rehabilitation period, is provided in the scientific article entitled *"Combined Creatine and Protein Supplementation in Conjunction with Resistance Training Promotes Muscle GLUT-4 Content and Glucose Tolerance in Humans,"* J. Appl. Physiol. 94: 1910-1916, 2003. The article reports a double-blind study that was performed on young healthy volunteers in which their right legs were immobilized for two weeks, followed by a six week rehabilitation period. The creatine group ingested 5 g of creatine 3 times daily during the immobilization period, with the dosage decreasing to 2.5 g once daily during the rehabilitation period. This relatively small dosage of creatine during rehabilitation resulted in a significant increase in muscle GLUT-4 (a glucose transporter protein) and glycogen content of the affected muscle when that muscle was subjected to a rehabilitation program, compared to the control group that did not receive creatine.

Both studies reveal the critical feature of the claimed invention which results in the new and unexpected results observed: chronic administration of a relatively high dose of creatine during the period in which a muscle is immobilized, which dosage is decreased to a substantially lower level during the rehabilitation period, results in a significantly shortened rehabilitation time needed to restore muscle mass following disuse atrophy and indeed stimulates

muscle hypertrophy, and significantly increases glycogen content of the affected muscle as well as upregulating the synthesis of specific proteins involved in glucose transport.

Applicant submits that the data reported in the above-described peer-reviewed scientific articles provide proof of the new and unexpected results of the claimed invention and respectfully requests that the Examiner take judicial notice of its evidentiary value.

Applicant submits that amended claims 13 and 17 and new claims 21 and 22 are proper for entry after a final office action, because the chronic administration of decreasing dosages of creatine for the treatment of muscle disuse syndrome is the same invention which was previously searched, but now the dosing regimen has been stated more particularly. Entry and allowance of amended claims 13 and 17 and new claims 21 and 22 are respectfully requested.

For all the foregoing reasons, amended claims 13 and 17 and new claims 21 and 22 are patentable over the cited prior art and in condition for allowance. Withdrawal of the asserted rejections and allowance of all pending claims 13-18 and 21-22 is respectfully requested.

Respectfully submitted,

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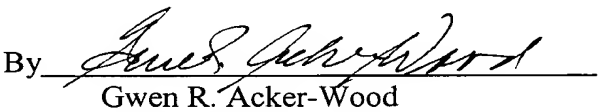
By 

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